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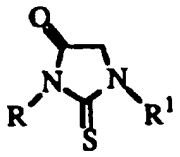
(54) Title: 2-THIOXO-IMIDAZOLIDIN-4-ONE DERIVATIVES AND THEIR USE FOR INCREASING HDL CHOLESTEROL CONCENTRATION

(57) Abstract

Compounds and a method for increasing the HDL cholesterol concentration in the blood of a mammal in need of increased HDL cholesterol blood concentration, which comprises administering to said mammal, orally or parenterally, a compound of formula (I) wherein R is alkyl; a substituted or unsubstituted aromatic N, O or S heterocycle; substituted or unsubstituted aryl, arylalkyl, benzhydryl or indanyl, in which the substituents are one to three members independently selected from the group consisting of alkyl, alkoxy, alkylthio, alkenyl, alkynyl, halo, perfluoroalkyl, perfluoroalkoxy or hydroxy; and R^1 is aryl, alkyl, alkenyl, alkynyl or substituted aryl where the substituents are one to three members independently selected from the group consisting of alkyl, alkoxy, alkylthio, alkenyl, alkynyl, halo, perfluoroalkyl, perfluoroalkoxy or hydroxy.



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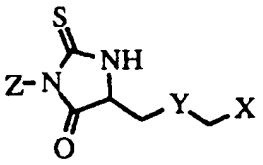
2-THIOXO-IMIDAZOLIDIN-4-ONE DERIVATIVES AND THEIR USE FOR INCREASING HDL CHOLESTEROL CONCENTRATION.

The present invention relates to compounds for increasing HDL cholesterol concentration in the blood of a mammal, to their use in this method of treatment, to pharmaceutical compositions containing the compounds and to a process for preparation of the compounds.

Numerous studies have demonstrated that both the risk of coronary heart disease (CHD) in humans and the severity of experimental atherosclerosis in animals are inversely correlated with serum HDL cholesterol (HDL-C) concentrations (Russ et al, Am. J. Med., 11 (1951) 480-493; Gofman et al, Circulation, 34 (1966) 679-697; Miller and Miller, Lancet, 1 (1975) 16-19; Gordon et al, Circulation, 79 (1989) 8-15; Stampfer et al, N. Engl. J. Med., 325 (1991) 373-381; Badimon et al, Lab. Invest., 60 (1989) 455-461). Atherosclerosis is the process of accumulation of cholesterol within the arterial wall which results in the occlusion, or stenosis, of coronary and cerebral arterial vessels and subsequent myocardial infarction and stroke. Angiographical studies have shown that elevated levels of some HDL particles appears to be correlated with a decrease in the number of sites of stenosis in the coronary arteries of humans (Miller et al, Br. Med. J., 282 (1981) 1741-1744).

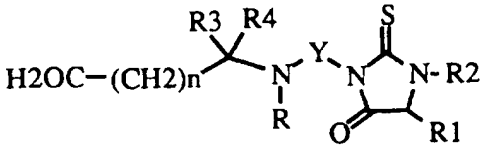
There are several mechanisms by which HDL may protect against the progression of atherosclerosis. Studies in vitro have shown that HDL is capable of removing cholesterol from cells (Picardo et al, Arteriosclerosis, 6 (1986) 434-441). Data of this nature suggests that one antiatherogenic property of HDL may lie in its ability to deplete tissues of excess free cholesterol and eventually lead to the delivery of this cholesterol to the liver (Glomset, J. Lipid Res., 9 (1968) 155-167). This has been supported by experiments showing efficient transfer of cholesterol from HDL to the liver (Glass et al, Circulation, 66 (Suppl. I) (1982) 102; MacKinnon et al, J. Biol. Chem., 261 (1986) 2548-2552). In addition, HDL may serve as a reservoir in the circulation for apoproteins necessary for the rapid metabolism of triglyceride-rich lipoproteins (Grow and Fried, J. Biol. Chem., 253 (1978) 1834-1841; Lagocki and Scanu, J. Biol. Chem., 255 (1980) 3701-3706; Schaefer et al, J. Lipid Res., 23 (1982) 1259-1273). Accordingly, agents which increase HDL cholesterol concentrations are useful as anti-atherosclerotic agents, particularly in the treatment of dyslipoproteinemias and coronary heart disease.

US 5,137,904 discloses a group of thiohydantoin derivatives of the formula



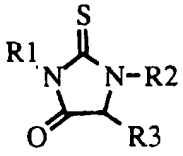
in which Z is alkyl, phenylalkyl, phenyl or substituted phenyl, where the substituent is a halogen, alkyl, alkoxy or halogenated alkyl group; X is phenyl, halophenyl, alkyl, alkenyl, or alkynyl; and Y is S or O. These compounds inhibit collagen-induced and ADP-induced platelet aggregation.

EP 0584694 andWO 93/18057 disclose a group of imidazolidin-3-yl benzoyl or alkanoyl amino acid derivatives as inhibitors of cell-cell adhesion for use in inhibition of thrombocyte aggregation, metastasis and osteoclast formation. Chronic administration for prevention of arteriosclerosis and thrombosis is disclosed.



in which Y = $-(CH_2)_n-CO-$ or -Ph-CO- .

JP 04,297,461 discloses a group of 2-thiohydantoin compounds of the following formula, said to be useful as anti-bacterial, anti-viral, anti-inflammatory and anti-rheumatic agents:

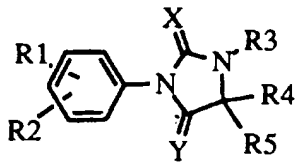


where R^1 is lower alkyl, lower alkenyl, phenyl(lower)alkyl or substituted phenyl with 1-3 groups chosen from lower alkyl, lower alkoxy, halogen, lower alkoxycarbonyl or hydroxy;

R^2 is either hydrogen or alkanoyl; and

R^3 is hydrogen, lower alkyl, phenyl, phenyl (lower) alkyl, or a lower alkylthio, lower alkyl group that can be substituted with one to three phenyl groups that have had a lower alkoxy group.

EP 0578516 discloses a group of 2-thiohydantoins, said to be useful anti-androgenic agents for treatment of various cancer, of the formula :



where X is oxygen or sulfur;

Y is oxygen, sulfur or NH

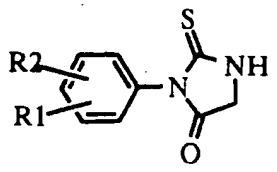
R^1 and R^2 are cyano, nitro, halogen, trifluoromethyl, or a free or esterified carboxylic acid or salt;

R^3 is hydrogen, alkyl, alkenyl, alkynyl, aryl or aryl-alkyl;

R^4 and R^5 are hydrogen, optionally substituted alkyl, or cycloalkyl.

US 5,411,981 discloses compounds closely related to EP 0578516, supra, where R^4 and R^5 are both methyl.

US 3,923,994 discloses a group of 3-aryl-2-thiohydantoin derivatives of the following formula, which have anti-arthritic activity:

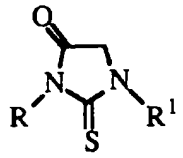


where R^1 and R^2 are hydrogen, chloro, bromo, fluoro or alkyl of 1-2 carbon atoms.

JP 73 87,030 discloses a group of 3-phenyl-2-thiohydantoin derivatives useful as herbicides.

US 4,473,393 discloses a group of pesticidal thiohydantoin compositions.

In accordance with this invention there is provided a compound of formula I:



I

wherein

R is alkyl of 1 to 6 carbon atoms; a substituted or unsubstituted aromatic N, O or S heterocycle having 4 to 6 carbon and one hetero ring members; substituted or unsubstituted aryl of 6 to 10 carbon atoms, arylalkyl of 7 to 12 carbon atoms, benzhydryl or indanyl , in which the substituents are one to three members independently selected from the group consisting of alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon ations, alkylthio of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, alkynyl of 2 to 6 carbon atoms, halo, perfluoroalkyl of 1 to 6 carbon atoms, perfluoroalkoxy of 1 to 6 carbon atoms or hydroxy; and

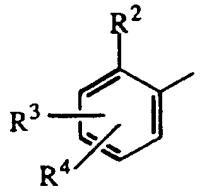
R^1 is aryl of 6 to 10 carbon atoms, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, alkynyl of 2 to 6 carbon atoms or substituted aryl of 6 to 10 carbon atoms where the substituents are one to three members independently selected from the group consisting of alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon ations, alkylthio of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, alkynyl of 2 to 6 carbon atoms, halo, perfluoroalkyl of 1 to 6 carbon atoms, perfluoroalkoxy of 1 to 6 carbon atoms or hydroxy, for use in the treatment of mammals.

A preferred embodiment of the invention provides a compound of formula I in which R is substituted phenyl where the substituents are two members of the group consisting of alkyl of 1 to 6 carbon atoms, perfluoroalkoxy of 1 to 6 carbon atoms, halo, or ortho substituted trimethylene or tetramethylene and R^1 is alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms or alkynyl of 2 to 6 carbon atoms.

Another preferred embodiment of the invention provides a compound of formula I in which R is substituted phenyl where the substituents are a halo and an alkyl group of 1 to 3 carbon atoms or ortho substituted trimethylene and R^1 is alkyl of 1 to 3 carbon atoms, alkenyl of 2 to 4 carbon atoms or alkynyl of 2 to 4 carbon atoms.

Another preferred embodiment of the invention provides a compound of formula I in which R is substituted phenyl where the substituents are chloro or fluoro in the 4- or 5- position and an alkyl group of 1 to 3 carbon atoms and R^1 is alkyl of 1 to 3 carbon atoms, alkenyl of 2 to 4 carbon atoms or alkynyl of 2 to 4 carbon atoms.

Certain of the compounds of the present invention are novel and comprise a further aspect of the present invention. Thus, according to a further aspect of the present invention there is provided a compound of formula I as described above wherein R^1 is alkyl of 1 to 6 carbon atoms and R is alkyl of 1 to 6 carbon atoms, naphthyl, benzhydryl, fluorophenylmethyl, phenethyl, 1-(fluorophenyl)ethyl, 5-chloro-2-methoxyphenyl, trifluoromethoxyphenyl, trifluoromethylphenyl, methylsulfanyl-phenyl, pyridyl or the group of formula II



II

where R^2, R^3 and R^4 together are 2-chloro, 4-fluoro, 2,4-chloro or 2,6- chloro, or R^2 is hydrogen, R^3 is a halogen in 3-position and R^4 is alkyl of 1 to 6 carbon atoms in 4-position, or R^2 is alkyl of 1 to 6 carbon atoms and R^3 and R^4 are, independently, hydrogen or alkyl of 1 to 6 carbon atoms or R^3 is a halogen and R^4 is hydrogen;

or

R^1 is alkenyl of 2 to 6 carbon atoms, R is is the group of formula II

where R^2 is alkyl of 1 to 6 carbon atoms and R^3 and R^4 are, independently, hydrogen or alkyl of 1 to 6 carbon atoms, or R^2 is hydrogen and R^3 and R^4 taken together are ortho substituted trimethylene or tetramethylene, or R^2 is alkyl of 1 to 6 carbon atoms, R^3 is halogen and R^4 is hydrogen, or R^2 is hydrogen, R^3 is halogen in 3-position and R^4 is alkyl of 1 to 6 carbon atoms in 4-position;

or

when R^1 is alkynyl of 2 to 6 carbon atoms, R is a group of formula II

where any two of R^2, R^3 and R^4 are, independently, alkyl of 1 to 6 carbon atoms, halo, perfluoralkyl of 1 to 6 carbon atoms, perfluoralkoxy of 1 to 6 carbon atoms, or, taken together, are ortho substituted trimethylene or tetramethylene;

or

when R^1 is aryl of 6 to 10 carbon atoms or arylalkyl of 7 to 12 carbon atoms, R is the group of formula II

where R^2 is alkyl of 1 to 6 carbon atoms, R^3 is a halogen and R^4 is hydrogen, or R^2 is hydrogen, R^3 is a halogen in 3-position and R^4 is alkyl of 1 to 6 carbon atoms in 4-position.

When any of R, R^1, R^2, R^3 or R^4 is alkyl it is preferably alkyl of 1 to 3 carbon atoms, especially methyl or ethyl, or any two of R^2, R^3 and R^4 when taken together are ortho substituted trimethylene or tetramethylene.

When R^1 is alkenyl of 2 to 6 carbon atoms it is preferably allyl,

When R^2 or R^3 are halogen they are preferably independently, chlorine or fluorine, especially in the 2-, 4-, and/or -6 positions. When R^2 or R^3 are perfluoralkyl of 1 to 6 carbon atoms, perfluoralkoxy of 1 to 6 carbon atoms

When R^1 is alkynyl of 2 to 6 carbon atoms it is preferably ethynyl, propargyl or butynyl, especially prop-2-ynl.

When R is aryl of 6 to 10 carbon atoms it is preferably, phenyl or naphthyl, the latter being preferably, 2-naphthyl. When R is aralkyl of 7 to 12 carbon atoms, it is preferably benzyl or phenethyl.

When R is fluorophenylmethyl, it is preferably 4-fluorophenylmethyl.

When R is 1-(fluorophenyl)ethyl, it is preferably 1-(4-fluorophenyl)ethyl.

When R is trifluoromethoxyphenyl, it is preferably 4-trifluoro-methoxyphenyl.

When R is methylsulfanylphenyl, it is preferably 2-methylsulfanylphenyl.

When R is pyridyl, it is preferably 3-pyridyl.

The most preferred compounds of this invention based upon their potency and overall activity profile in the standard experimental test model are:

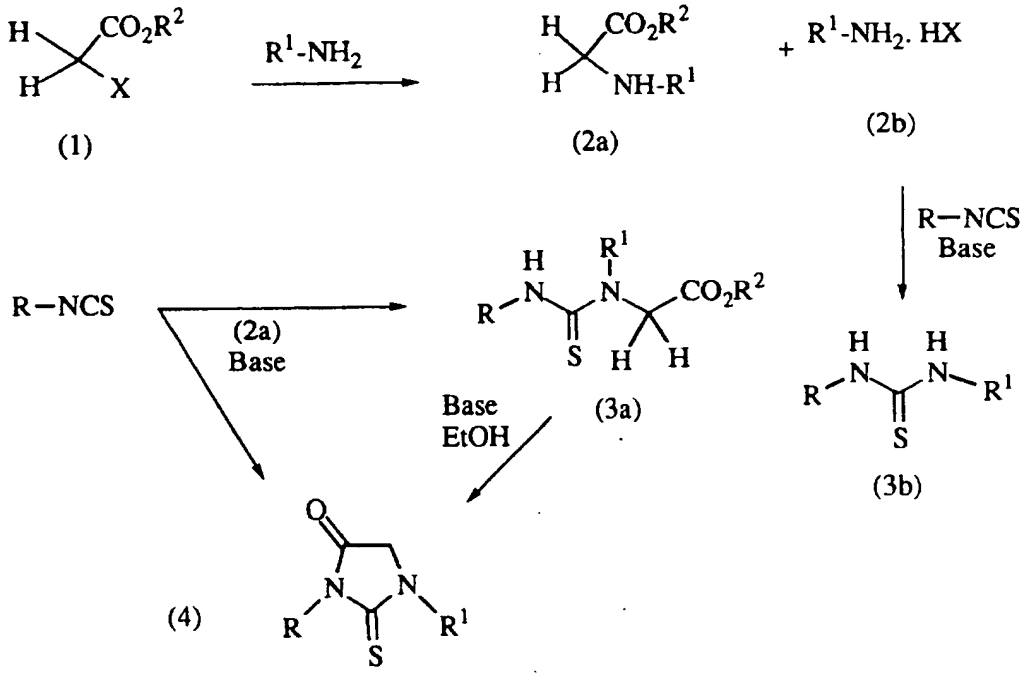
3-(5-Chloro-2-methylphenyl)-1-methyl-2-thioxo-imidazolidin-4-one
3-(3-Chloro-2-methylphenyl)-1-methyl-2-thioxo-imidazolidin-4-one
3-(4-Chloro-2-methylphenyl)-1-methyl-2-thioxo-imidazolidin-4-one
3-(Indan-5-yl)-1-methyl-2-thioxo-imidazolidin-4-one
3-(2,6-Diisopropylphenyl)-1-methyl-2-thioxo-imidazolidin-4-one
3-(2-Ethyl-6-isopropylphenyl)-1-methyl-2-thioxo-imidazolidin-4-one
3-(2-Ethyl-6-methylphenyl)-1-methyl-2-thioxo-imidazolidin-4-one
3-(5-Chloro-2-methylphenyl)-1-ethyl-2-thioxo-imidazolidin-4-one
3-(2,6-Dichlorophenyl)-1-ethyl-2-thioxo-imidazolidin-4-one
1-Ethyl-3-(4-fluorophenyl)--2-thioxo-imidazolidin-4-one

1-Ethyl-2-thioxo-3-(4-trifluoromethoxyphenyl)-imidazolidin-4-one
3-(2,6-Dimethylphenyl)-1-ethyl-2-thioxo-imidazolidin-4-one
1-Ethyl-3-isobutyl-2-thioxo-imidazolidin-4-one
3-(2-Chlorophenyl)-1-ethyl-2-thioxo-imidazolidin-4-one
1-Ethyl-3-(2-tolyl)-2-thioxo-imidazolidin-4-one
3-(2-Chloro-6-methylphenyl)-1-ethyl-2-thioxo-imidazolidin-4-one
1-Ethyl-3-(5-fluoro-2-methylphenyl)-2-thioxo-imidazolidin-4-one
3-(2,6-Diisopropylphenyl)-1-ethyl-2-thioxo-imidazolidin-4-one
1-Ethyl-2-thioxo-3-(2-trifluoromethylphenyl)-imidazolidin-4-one
1-Ethyl-3-(2-ethyl-6-methylphenyl)-2-thioxo-imidazolidin-4-one
3-(2-Chloro-4-methylphenyl)-1-ethyl-2-thioxo-imidazolidin-4-one
3-(2,4-Dichlorophenyl)-1-ethyl-2-thioxo-imidazolidin-4-one
3-(2,4-Dimethylphenyl)-1-ethyl-2-thioxo-imidazolidin-4-one
3-(2,5-Dimethylphenyl)-1-ethyl-2-thioxo-imidazolidin-4-one
1-Ethyl-2-thioxo-3-(2,4,5-trimethylphenyl)-imidazolidin-4-one
1-Ethyl-3-(2-isopropylphenyl)-2-thioxo-imidazolidin-4-one
1-Ethyl-3-(2-ethylphenyl)-2-thioxo-imidazolidin-4-one
3-(5-Chloro-2-methylphenyl)-1-phenyl-2-thioxo-imidazolidin-4-one
3-(5-Chloro-2-methylphenyl)-1-isopropyl-2-thioxo-imidazolidin-4-one
3-(2,6-Dimethylphenyl)-1-isopropyl-2-thioxo-imidazolidin-4-one
3-(2-Ethyl-6-methylphenyl)-1-isopropyl-2-thioxo-imidazolidin-4-one
1-Butyl-3-(4-fluorophenyl)-2-thioxo-imidazolidin-4-one
1-Allyl-3-(2,6-dimethylphenyl)-2-thioxo-imidazolidin-4-one
3-(2,6-Dimethylphenyl)-1-(prop-2-ynyl)-2-thioxo-imidazolidin-4-one
3-(3-Chloro-4-methylphenyl)-1-methyl-2-thioxo-imidazolidin-4-one
3-(2-Ethylphenyl)-1-methyl-2-thioxo-imidazolidin-4-one
1-Methyl-3-(2-isopropylphenyl)-2-thioxo-imidazolidin-4-one
3-(4-t-Butylphenyl)-1-methyl-2-thioxo-imidazolidin-4-one
1-Allyl-3-(5-chloro-2-methylphenyl)-2-thioxo-imidazolidin-4-one
3-(5-Chloro-2-methylphenyl)-1-(prop-2-ynyl)-2-thioxo-imidazolidin-4-one
1-Ethyl-3-(2-ethyl-6-isopropylphenyl)-2-thioxo-imidazolidin-4-one.

A preferred use of the compounds of formula I or method of treatment using the compounds is for increasing HDL cholesterol concentration in the blood of a mammal, by administering to said mammal an amount of a substituted 2-thioxo-imidazolidin-4-

one as herein defined, sufficient to increase that HDL cholesterol concentration, and this represents further aspects of the present invention.

The compounds of the invention can be prepared readily according to the following reaction scheme or modification thereof using readily available starting materials, reagents and conventional synthetic procedures. It is also possible to make use of variants of these process steps, which in themselves are known to and well within the preparatory skill of the medicinal chemist. In the following reaction scheme, R^2 is hydrogen or alkyl of 1 to 6 carbon atoms and X is a halogen.



N-Substituted amino acids (2a) were prepared by reacting the corresponding α-halo acids (1) with the appropriate amines (excess). The reaction was carried out either neat or in water at ambient temperature for 18 hours. One equivalent of the amine scavenges the hydrohalide formed during the alkylation forming the amine hydrohalide (2b) as a side product. The N-alkyl amino acids (2a) were either purified by crystallization from an appropriate solvent, or reacted with the isothiocyanates as crude product mixtures containing the amine hydrohalide salt. Reaction of 2a with isothiocyanates is carried out in chloroform or methylene chloride in the presence of a

base such as triethyl amine. The mixture is heated at reflux for 3 to 18 hours. The reaction affords either the thiourea (3a) or the thiohydantoin (4) directly (depending on the nature of R^1). Cyclization of 3a to the thiohydantoin (4) is accomplished by refluxing in ethanol for 2 to 3 hours in the presence of base (triethyl amine). In the case of reacting the crude product mixture (2a & 2b) with isothiocyanates, the thiourea (3b) is formed as a side product along with 4. Purification of 4 was achieved by 1) fractional crystallization, 2) flash chromatography, 3) extracting 3b in 2N hydrochloric acid or 4) precipitating 3b as its hydrochloride salt from an appropriate solvent such as ethyl acetate or diethyl ether.

This invention also provides pharmaceutical compositions comprised of the 2-thioxo imidazolidin-4-one derivatives either alone or in combination with excipients (i.e. pharmaceutically acceptable materials with no pharmacological effects). Such compositions are useful in the treatment of atherosclerotic conditions such as dyslipoproteinemias and coronary heart disease, in that they increase the blood serum high density lipoprotein concentration of mammals treated with the compounds.

The precise dosage to be employed depends upon several factors including the host, whether in veterinary medicine or human medicine, the nature and severity of the condition being treated, the mode of administration and the particular active substance employed. The compounds may be administered by any conventional route, in particular enterally, preferably orally in the form of tablets or capsules. Administered compounds can be in the free form or pharmaceutically acceptable salt form as appropriate, for use as a pharmaceutical, particularly for use in the prophylactic or curative treatment of atherosclerosis and sequelae (angina pectoris, myocardial infarction, arrhythmias, heart failure, kidney failure stroke, peripheral arterial occlusion, and related disease states). These measures will slow the rate of progress of the disease state and assist the body in reversing the process direction in a natural manner.

Any suitable carrier known to the art can be used to prepare the pharmaceutical compositions. In such a composition, the carrier may be a solid, liquid or mixture of a solid and a liquid. Solid compositions include powders, tablets and capsules. A solid carrier can be one or more substances which may also act as a flavoring agent, lubricant, solubilizer, suspending agent, binder, or tablet disintegrant. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets the active ingredient is mixed with a carrier having the necessary

binding properties in suitable proportions and compacted in the shape and size desired. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, hydroxymethyl cellulose, sodium carboxymethyl cellulose, a low melting wax, cocoa butter, and the like. Encapsulating materials may also be employed with the compounds of this invention, and the term "composition" is intended to include the active ingredient in combination with an encapsulating material as a formulation, with or without other carriers. Cachets may also be used in the delivery of the anti-atherosclerotic medicament of this invention.

Sterile liquid compositions include solutions, suspensions, emulsions, syrups and elixirs. The compounds of this invention may be dissolved or suspended in the pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent or a mixture of both. Preferably the liquid carrier is one suitable for parental injection. Where the compounds are sufficiently soluble they can be dissolved directly in normal saline with or without the use of suitable organic solvents , such as propylene glycol or polyethylene glycol. If desired, dispersions of the finely divided compounds can be made-up in aqueous starch or sodium carboxymethyl cellulose solution, or in a suitable oil, such as arachis oil. Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by intramuscular, intraperitoneal or subcutaneous injection. In many instances a liquid composition form may be used instead of the preferred solid oral method of administration.

It is preferred to prepare unit dosage forms of the compounds for standard administration regimens. In this way, the composition can be subdivided readily into smaller doses at the physicians direction. For example, unit dosages may be made up in packeted powders, vials or ampoules and preferably in capsule or tablet form. The active compound present in these unit dosage forms of the composition may be present in an amount of from about one gram to about fifteen grams or more, for single or multiple daily administration, according to the particular need of the patient. The daily dose of active compound will vary depending upon the route of administration, the size, age and sex of the patient, the severity of the disease state, and the response to the therapy as traced by blood analysis and the patients recovery rate. By initiating the treatment regimen with a minimal daily dose of about one gram, the blood levels of HDL and the patients symptomatic relief analysis may be used to determine whether a larger dose is indicated. Based upon the data presented below, the projected daily dose

for both human and veterinary use will be from about 10 to about 200 milligrams/kilogram per day. However, in general, satisfactory results are indicated to be obtained at daily dosages in the range of from 400 milligrams to about 2000 milligrams, conveniently administered in divided doses two to four times a day.

The ability of the compounds of this invention to increase blood serum HDL levels was established by the following standard experimental procedure for determination of HDL cholesterol:

Male Sprague-Dawley rats weighing 200-225 g are housed two per cage and fed Purina Rodent Chow Special Mix 5001-S supplemented with 0.25 % cholic acid and 1.0 % cholesterol and water ad libitum for 8 days. Each test substance is administered to a group of six rats fed the same diet with the test diet mixed in as 0.005 - 0.1 % of the total diet. Body weight and food consumption are recorded prior to diet administration and at termination. Typical doses of the test substances are 5 - 100 mg/kg/day.

At termination, blood is collected from anesthetized rats and the serum is separated by centrifugation. Total serum cholesterol is assayed using the Sigma Diagnostics enzymatic kit for the determination of cholesterol, Sigma Procedure No. 352, modified for use with ninety-six well microtiter plates. After reconstitution with water the reagent contains 300 U/l cholesterol oxidase, 100 U/l cholesterol esterase, 1000 U/l horse radish peroxidase, 0.3 mmoles/l 4-aminoantipyrine and 30.0 mmoles/l p-hydroxybenzenesulfonate in a pH 6.5 buffer. In the reaction cholesterol is oxidized to produce hydrogen peroxide which is used to form a quinoneimine dye. The concentration of dye formed is measured spectrophotometrically by absorbance at 490 nm after incubation at 25C for 30 minutes. The concentration of cholesterol was determined for each serum sample relative to a commercial standard from Sigma.

HDL cholesterol concentrations in serum are determined by separation of lipoprotein classes by fast protein liquid chromatography (FPLC) by a modification of the method of Kieft et al., J. Lipid Res., 32 (1991) 859-866. 25 ul of serum is injected onto Superose 12 and Superose 6 (Pharmacia), in series, with a column buffer of 0.05 M Tris (2-amino-2-hydroxymethyl-1,3-propanediol) and 0.15 M sodium chloride at a flow rate of 0.5 ml/min. The eluted sample is mixed on line with Boehringer-Mannheim cholesterol reagent pumped at 0.2 ml/min. The combined eluents are mixed and incubated on line through a knitted coil (Applied Biosciences) maintained at a temperature of 45C. The eluent is monitored by measuring absorbance at 490 nm and

gives a continuous absorbance signal proportional to the cholesterol concentration. The relative concentration of each lipoprotein class is calculated as the per cent of total absorbance. HDL cholesterol concentration, in serum, is calculated as the per cent of total cholesterol as determined by FPLC multiplied by the total serum cholesterol concentration.

Test compounds were administered at a dose of 100 mg/kg. The duration of treatment was eight days. The compounds of the present invention increase HDL cholesterol concentrations as summarized in Table I:

Table I

Compound of Example	HDL Cholesterol Level Increase (%)
1	159
2	57
3	29
4	39
5	150
6	101
7	202
8	112
9	89
10	141
11	203
12	84
13	222
14	203
15	92
16	132
17	142
18	59
19	39
20	265

Table I (Continued)

Compound of Example	HDL Cholesterol Level Increase (%)
21	180
22	26
23	95
24	157
25	163
26	65
27	222
28	112
29	54
30	115
31	167
32	112
33	66
34	49
35	98
36	30
37	49
38	83
39	124
40	112
41	202
42	237
43	78
44	39
45	127

Table I (Continued)

Compound of Example	HDL Cholesterol Level Increase (%)
46	146
47	24
48	64
49	52
50	77
51	88
52	100
53	47
54	71
55	87
56	53
57	183
58	62
59	177
60	74
61	325
62	204
63	

The following examples are presented to illustrate the production of representative compounds useful in the method of this invention, rather than as a limit to the scope of applicant's invention:

EXAMPLE 1

3-(5-Chloro-2-methylphenyl)-1-methyl-2-thioxo-imidazolidin-4-one

A mixture of sarcosine ethyl ester hydrochloride (7.68 g), 5-chloro-2-methylphenyl-isothiocyanate (9.18 g), triethyl amine (12 g) and chloroform (200 mL) was heated at reflux for 5 hours. The mixture was cooled to ambient temperature,

washed with 1N HCl (2x200 mL), then with water (200 mL) The organic phase was evaporated to dryness. The residue was crystallized from ethanol to give the title compound (9.2 g) as a tan solid, m.p. 132-134° C. Anal. Calcd. for C_{11} H_{11} Cl N_2 O S: C, 51.87; H, 4.35; N,11.00. Found: C, 51.79; H, 4.12; N, 10.73. Mass spectrum (EI, $M.^+$) *m/z* 254/256.

EXAMPLE 2

3-Benzhydryl-1-methyl-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 1 using 11.25 g of benzhydryl-isothiocyanate, 7.68 g of sarcosine ethyl ester hydrochloride, 12 g of triethyl amine, and 200 mL of chloroform. The title compound was obtained (7.40 g) as an off-white solid, m.p. 139-141° C. Anal. Calcd. for C_{17} H_{16} N_2 O S: C, 68.89; H, 5.44; N, 9.45. Found: C, 68.92; H, 5.43; N, 9.58. Mass spectrum (EI, $M.^+$) *m/z* 296.

EXAMPLE 3

1-Methyl-3-(pyridin-3-yl)-2-thioxo-imidazolidin-4-one

A mixture of sarcosine ethyl ester hydrochloride (7.68 g), pyridin-3-yl-isothiocyanate (6.8 g), triethyl amine (10.1 g) and chloroform (200 mL) was heated at reflux for 3.5 hours. The solvent was evaporated. The residue was dissolved in ethyl acetate (300 mL) and washed with water (2x200 mL). The organic phase was dried over anhydrous magnesium sulfate. The solvent was evaporated. Crystallization from ethyl acetate afforded the title compound (4.1 g) as an off-white solid, m.p. 149-151° C. Anal. Calcd. for C_9 H_9 N_3 O S: C, 52.16; H, 4.38; N, 20.28. Found: C, 52.16; H, 4.05; N, 20.06. Mass spectrum (EI, $M.^+$) *m/z* 207.

EXAMPLE 4

3-(5-Chloro-2-methoxyphenyl)-1-methyl-2-thioxo-imidazolidin-4-one

A mixture of sarcosine ethyl ester hydrochloride (7.68 g), 5-chloro-2-methoxyphenyl-isothiocyanate (10.0 g), triethyl amine (10.0 g) and chloroform (150 mL) was heated at reflux for 4.5 hours. The mixture was cooled to ambient

temperature. The precipitated solid was collected, washed with chloroform and air dried to give the title compound (11.8 g) as an off-white solid, m.p. 245-247° C. Anal. Calcd. for C_{11} H_{11} Cl N_2 O_2 S: C, 48.80; H, 4.10; N,10.35. Found: C, 48.42; H, 3.96; N, 10.33. Mass spectrum (EI, $M.^+$) *m/z* 270.

EXAMPLE 5

3-(3-Chloro-2-methylphenyl)-1-methyl-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 1 using 13.2 g of 3-chloro-2-methylphenyl-isothiocyanate, 11.0 g of sarcosine ethyl ester hydrochloride, 25 g of triethyl amine, and 300 mL of chloroform. Crystallization from diethyl ether afforded the title compound (15.2 g) as a tan solid, m.p. 122-124° C. Anal. Calcd. for C_{11} H_{11} Cl N_2 O S: C, 51.87; H, 4.35; N,11.00. Found: C, 51.96; H, 4.21; N, 11.05. Mass spectrum (EI, $M.^+$) *m/z* 254/256.

EXAMPLE 6

3-(3-Chloro-4-methylphenyl)-1-methyl-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 1 using 18.3 g of 3-chloro-4-methylphenyl-isothiocyanate, 15.3 g of sarcosine ethyl ester hydrochloride, 25 g of triethyl amine, and 300 mL of chloroform. Crystallization from ethyl acetate afforded the title compound (14.5 g) as an off-white solid, m.p. 178-180° C. Anal. Calcd. for C_{11} H_{11} Cl N_2 O S: C, 51.87; H, 4.35; N,11.00. Found: C, 51.89; H, 4.20; N, 10.95. Mass spectrum (+FAB, $[M+H]^+$) *m/z* 255/257.

EXAMPLE 7

3-(4-Chloro-2-methylphenyl)-1-methyl-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 1 using 9.18 g of 4-chloro-2-methylphenyl-isothiocyanate, 7.68 g of sarcosine ethyl ester hydrochloride, 12.0 g of triethyl amine, and 300 mL of chloroform. Crystallization from diethyl ether afforded the title compound (7.5 g) as an off-white solid, m.p. 113-115° C. Anal. Calcd. for C_{11} H_{11} Cl N_2 O S: C, 51.87; H, 4.35; N,11.00. Found: C, 51.72; H, 4.17; N, 10.88. Mass spectrum (EI, $M.^+$) *m/z* 254/256.

EXAMPLE 8

3-(Indan-5-yl)-1-methyl-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 1 using 7.7 g of indan-5-yl-isothiocyanate, 6.7 g of sarcosine ethyl ester hydrochloride, 12 g of triethyl amine, and 300 mL of chloroform. Crystallization from ethyl acetate afforded the title compound (7.9 g) as a tan solid, m.p. 158-160° C. Anal. Calcd. for $C_{13}H_{14}N_2OS$: C, 63.39; H, 5.73; N,11.37. Found: C, 63.30; H, 5.81; N, 11.31. Mass spectrum (EI, $M.^+$) *m/z* 246.

EXAMPLE 9

3-(2,6-Diisopropylphenyl)-1-methyl-2-thioxo-imidazolidin-4-on.

The title compound was prepared by the procedure described in Example 1 using 8.3 g of 2,6-diisopropylphenyl-isothiocyanate, 5.8 g of sarcosine ethyl ester hydrochloride, 14.5 g of triethyl amine, and 200 mL of chloroform. Crystallization from diethyl ether/hexane mixture afforded the title compound (6.6 g) as a tan solid, m.p. 174-176° C. Anal. Calcd. for $C_{16}H_{22}N_2OS$: C, 66.17; H, 7.63; N, 9.64. Found: C, 66.39; H, 7.63; N, 9.59. Mass spectrum (+FAB, $[M+H]^+$) *m/z* 269/271.

EXAMPLE 10

3-(2-Ethyl-6-isopropylphenyl)-1-methyl-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 1 using 10.25 g of 2-ethyl-6-isopropylphenyl-isothiocyanate, 7.68 g of sarcosine ethyl ester hydrochloride, 14.8 g of triethyl amine, and 200 mL of chloroform. Crystallization from diethyl ether/hexane mixture afforded the title compound (8.95 g) as a tan solid, m.p. 132-134° C. Anal. Calcd. for $C_{15}H_{20}N_2OS$: C, 65.18; H, 7.29; N, 10.13. Found: C, 65.11; H, 7.31; N, 10.05. Mass spectrum (PBEI, $M.^+$) *m/z* 276.

EXAMPLE 11

3-(2-Ethyl-6-methylphenyl)-1-methyl-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 1 using 8.9 g of 2-ethyl-6-methylphenyl-isothiocyanate, 7.68 g of sarcosine ethyl ester hydrochloride, 12.5 g of triethyl amine, and 250 mL of chloroform. Crystallization from diethyl ether afforded the title compound (7.45 g) as a peach solid, m.p. 106-108° C. Anal. Calcd. for $C_{13}H_{16}N_2OS$: C, 62.87; H, 6.49; N, 11.28. Found: C, 62.52; H, 6.61; N, 11.29. Mass spectrum (+ESI, $[M+H]^+$) *m/z* 269/271.

EXAMPLE 12

3-(2-Chloro-6-methylphenyl)-1-methyl-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 1 using 9.2 g of 2-chloro-6-methylphenyl-isothiocyanate, 7.68 g of sarcosine ethyl ester hydrochloride, 12 g of triethyl amine, and 200 mL of chloroform. Crystallization from ethanol afforded the title compound (7.1 g) as an orange solid (7.1 g), m.p. 142-145° C. Anal. Calcd. for. $C_{11}H_{11}ClN_2OS$: C, 51.87; H, 4.35; N,11.00. Found: C, 51.96; H, 4.26; N, 10.97. Mass spectrum (EI, $M.^+$) *m/z* 254.

EXAMPLE 13

3-(2-Ethylphenyl)-1-methyl-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 1 using 16.3 g of 2-ethylphenyl-isothiocyanate; 15.3 g of sarcosine ethyl ester hydrochloride, 20.2 g of triethyl amine, and 300 mL of chloroform. The title compound (20.4 g) was obtained as an off-white solid, m.p. 135-137° C. Anal. Calcd. for $C_{12}H_{14}N_2OS$: C, 61.51; H, 6.02; N,11.96. Found: C, 61.11; H, 5.92; N, 11.71. Mass spectrum (EI, $M.^+$) *m/z* 234.

EXAMPLE 14

1-Methyl-3-(2-isopropylphenyl)-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 1 using 14.2 g of 2-isopropylphenyl-isothiocyanate, 12.29 g of sarcosine ethyl ester hydrochloride, 16.0 g of triethyl amine, and 200 mL of chloroform. Crystallization from diethyl ether afforded the title compound (15.9 g) as a peach solid, m.p. 129-131° C. Anal. Calcd. for $C_{13}H_{16}N_2OS$: C, 62.87; H, 6.49; N, 11.28. Found: C, 62.89; H, 6.38; N, 11.28. Mass spectrum (EI, $M.^+$) *m/z* 248.

EXAMPLE 15

3-(2,6-Dichlorophenyl)-1-methyl-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 1 using 14.28 g of 2,6-dichlorophenyl-isothiocyanate, 10.75 g of sarcosine ethyl ester hydrochloride, 14.5 g of triethyl amine, and 200 mL of chloroform. Crystallization from diethyl ether afforded the title compound (16.9 g) as a light peach solid, m.p. 207-209° C. Anal. Calcd. for $C_{10}H_8Cl_2N_2OS$: C, 43.65; H, 2.93; N, 10.18. Found: C, 43.57; H, 2.61; N, 10.14. Mass spectrum (EI, $M.^+$) *m/z* 274.

EXAMPLE 16

3-(5-Chloro-2-methylphenyl)-1-ethyl-2-thioxo-imidazolidin-4-one

2-Chloro acetic acid (27.5 g) was added portionwise while stirring to a 70% aqueous ethyl amine solution (500 mL). The addition was carried over a period of 30 minutes. The mixture was stirred at ambient temperature for 18 hours. The mixture was then evaporated to a viscous oily residue (55 g). The crude product consisted of a 1:1 mixture of N-ethyl glycine and ethyl amine hydrochloride. This product mixture was usedwithout further purification for the preparation of the title compound, in the next paragraph, and for preparation of the title compounds described in Example 17 through Example 42 and in Example 58.

A mixture of the crude N-ethyl glycine (9.23 g), 5-chloro-2-methylphenyl-isothiocyanate (9.18 g), triethyl amine (10 g) and chloroform (250 mL) was heated at

reflux for 18 hours. The solvent was evaporated. The residue was dissolved in ethyl acetate (400 mL) and water (300 mL). The organic phase was washed with 1N HCl (2x300 mL), then evaporated to dryness. Purification was achieved through crystallization from ethanol. The title compound (7.6 g) was obtained as a light pink solid, m.p. 152-154° C. Anal. Calcd. for. C_{12} H_{13} Cl N_2 O S: C, 53.63; H, 4.88; N, 10.42. Found: C, 53.36; H, 4.79; N, 10.35. Mass spectrum (EI, $M.^+$) *m/z* 268/270.

EXAMPLE 17

3-(2,6-Dichlorophenyl)-1-ethyl-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 16 using 10.2 g of 2,6-dichlorophenyl-isothiocyanate, 7.4 g of N-ethyl glycine, 10 g of triethyl amine, and 250 mL of chloroform. Purification was achieved through crystallization from ethanol. The title compound (6.5 g) was obtained as a tan solid, m.p. 170-172° C. Anal. Calcd. for. C_{11} H_{10} Cl_2 N_2 O S: C, 45.69; H, 3.48; N, 9.69. Found: C, 45.53; H, 3.19; N, 9.62. Mass spectrum (EI, $M.^+$) *m/z* 288/290/292.

EXAMPLE 18

1-Ethyl-3-(4-fluorophenyl)-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 16 using 7.65 g of 4-fluorophenyl-isothiocyanate, 9.32 g of N-ethyl glycine, 10 g of triethyl amine, and 250 mL of chloroform. Purification was achieved through crystallization from ethanol. The title compound (6.6 g) was obtained as a pink solid, m.p. 149-151° C. Anal. Calcd. for. C_{11} H_{11} F N_2 O S: C, 55.45; H, 4.65; N,11.76. Found: C, 55.31; H, 4.51; N, 10.82. Mass spectrum (EI, $M.^+$) *m/z* 238.

EXAMPLE 19

3-(5-Chloro-2-methoxyphenyl)-1-ethyl-2-thioxo-imidazolidin-4-one

A mixture N-ethyl glycine (9.2 g), 5-chloro-2-methoxyphenyl-isothiocyanate (10 g), triethylamine (10.1 g), methylene chloride (150 mL) was heated at reflux for 3.5 hours. The mixture was evaporated to dryness. The residue collected, washed with

hot ethanol and dried. Title compound (7.6 g) was obtained as a creamy solid, m.p. 171-174° C. Anal. Calcd. for. C_{12} H_{13} Cl N_2 O_2 S: C, 50.61; H, 4.60; N, 9.84. Found: C, 50.33; H, 4.50; N, 9.69. Mass spectrum (EI, $M.^+$) *m/z* 284/286.

EXAMPLE 20

1-Ethyl-2-thioxo-3-(4-trifluoromethoxyphenyl)-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 19 using 9.2 g of N-ethyl glycine, 10.9 g of 4-trifluoromethoxyphenyl-isothiocyanate, 10.1 g of triethylamine, and 150 mL of methylene chloride. Purification was achieved by flash chromatography on silica gel (methylene chloride). Title compound (4.6 g) was obtained as a creamy solid, m.p. 116-119° C. Anal. Calcd. for. C_{12} H_{11} F_3 N_2 O_2 S: C, 47.37; H, 3.64; N, 9.21. Found: C, 47.20; H, 3.50; N, 9.13. Mass spectrum (EI, $M.^+$) *m/z* 304.

EXAMPLE 21

3-(2,6-Dimethylphenyl)-1-ethyl-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 19 using 9.2 g of N-ethyl glycine, 8.2 g of 2,6-dimethylphenyl-isothiocyanate, 10.1 g of triethylamine, and 150 mL of methylene chloride. Purification was achieved through crystallization from ethanol. Title compound (2.3 g) was obtained as a white solid (2.3 g). m.p. 128-131° C. Anal. Calcd. for. C_{13} H_{16} N_2 O S: C, 62.87; H, 6.49; N, 11.28. Found: C, 62.83; H, 6.50; N, 11.25. Mass spectrum (EI, $M.^+$) *m/z* 248.

EXAMPLE 22

1-Ethyl-3-(4-fluorobenzyl)-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 19 using 9.2 g of N-ethyl glycine, 8.4 g of 4-fluorobenzyl-isothiocyanate, 10.1 g of triethylamine, and 150 mL of methylene chloride. Purification was achieved through crystallization from ethyl acetate/hexane mixture. Title compound (4.85 g) was obtained as a white solid, m.p. 73-76° C. Anal. Calcd. for. C_{12} H_{13} F N_2 O S: C, 57.12; H,

5.19; N, 11.10 Found: C, 56.97; H,5.15; N, 11.06. Mass spectrum (EI, $M.^+$) *m/z* 252.

EXAMPLE 23

1-Ethyl-3-isobutyl-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 19 using 9.2 g of N-ethyl glycine, 5.7 g of isobutyl-isothiocyanate, 10.1 g of triethylamine, and 150 mL of methylene chloride. Purification was achieved by flash chromatography on silica gel (methylene chloride). Title compound (2.3 g) was obtained as an oil. Anal. Calcd. for. $C_9 H_{16} N_2 O S$: C, 53.97; H, 8.05; N, 13.99. Found: C, 54.01; H, 8.21; N, 14.00. Mass spectrum (EI, $M.^+$) *m/z* 200.

EXAMPLE 24

3-(2-Chlorophenyl)-1-ethyl-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 19 using 9.2 g of N-ethyl glycine, 8.48 g of 2-chlorophenyl-isothiocyanate, 10.1 g of triethylamine, and 150 mL of methylene chloride. Purification was achieved through crystallization from ethanol. Title compound (3.85 g) was obtained as an orange solid, m.p. 142-145° C. Anal. Calcd. for. $C_{11} H_{11} Cl N_2 O S$: C, 51.87; H, 4.35; N, 11.00. Found: C, 51.96; H, 4.26; N, 10.97. Mass spectrum (EI, $M.^+$) *m/z* 254.

EXAMPLE 25

1-Ethyl-3-(2-tolyl)-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 19 using 9.2 g of N-ethyl glycine, 7.4 g of 2-tolyl-isothiocyanate, 10.1 g of triethylamine, and 150 mL of methylene chloride. Purification was achieved through crystallization from ethanol. Title compound (3.6 g) was obtained as a creamy solid, m.p. 105-108° C. Anal. Calcd. for. $C_{12} H_{14} N_2 O S$: C, 61.51; H, 6.02; N,11.93. Found: C, 61.22; H, 5.96; N, 11.89. Mass spectrum (EI, $M.^+$) *m/z* 234.

EXAMPLE 26

1-Ethyl-3-(naphthalen-2-yl)-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 19 using 9.2 g of N-ethyl glycine, 9.3 g of 2-naphthyl-isothiocyanate, 10.1 g of triethylamine, and 150 mL of methylene chloride. Purification was achieved through crystallization from ethanol. Title compound (4.7 g) was obtained as a light pink solid, m.p. 156-159° C. Anal. Calcd. for. C_{15} H_{14} N_2 O S: C, 66.64; H, 5.22; N, 10.36 Found: C, 66.69; H,5.24; N, 10.42. Mass spectrum (EI, $M.^+$) *m/z* 270.

EXAMPLE 27

3-(2-Chloro-6-methylphenyl)-1-ethyl-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 19 using 9.2 g of N-ethyl glycine, 9.1 g of 2-chloro-6-methylphenyl-isothiocyanate, 10.1 g of triethylamine, and 150 mL of methylene chloride. Purification was achieved by flash chromatography on silica gel (methylene chloride). Crystallization from ethanol afforded the title compound (5.4 g) as a creamy solid, m.p. 124-126° C. Anal. Calcd. for. C_{12} H_{13} Cl N_2 O S: C, 53.63; H, 4.87; N, 10.42. Found: C, 53.43; H, 4.79; N, 10.28. Mass spectrum (EI, $M.^+$) *m/z* 268/270.

EXAMPLE 28

1-Ethyl-3-(5-fluoro-2-methylphenyl)-2-thioxo-imidazolidin-4-one

A mixture of the crude N-ethyl glycine (11.5 g), 5-fluoro-2-methylphenyl-isothiocyanate (10.42 g), triethyl amine (12.5 g) and chloroform (300 mL) was heated at reflux for 6 hours. The solvent was evaporated. The residue was dissolved in ethyl acetate (500 mL) and washed with water (500 mL). The organic phase was evaporated to dryness. The residue was dissolved in ethanol (50 mL), then diluted with diethyl ether (200 mL). The solution was saturated with hydrogen chloride. The mixture was filtered. The solid was discarded. The filtrate was evaporated to dryness. The residue was dissolved in diethyl ether (300 mL) and washed with water (200 mL). The organic phase was dried over anhydrous sodium sulfate and evaporated to dryness. Crystallization from ethanol afforded the title compound (6.5 g) as a pink solid, m.p.

98-100° C. Anal. Calcd. for. C_{12} H_{13} F N_2 O S: C, 57.13; H, 5.19; N, 11.10. Found: C, 56.88; H, 5.17; N, 11.05. Mass spectrum (EI, $M.^+$) *m/z* 252.

EXAMPLE 29

3-(2,6-Diisopropylphenyl)-1-ethyl-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 16 using 21.9 g of 2,6-diisopropylphenyl-isothiocyanate, 18.4 g of N-ethyl glycine, 20.2 g of triethyl amine, and 300 mL of chloroform. Purification was achieved through crystallization from ethanol. The title compound (8.2 g) was obtained as light yellow solid, m.p. 159-161° C. Anal. Calcd. for. C_{17} H_{24} N_2 O S: C, 67.07; H, 7.94; N, 9.20. Found: C, 66.92; H, 8.03; N, 9.13. Mass spectrum (PBEI, $M.^+$) *m/z* 304.

EXAMPLE 30

1-Ethyl-2-thioxo-3-(2-trifluoromethylphenyl)-imidazolidin-4-one.

The title compound was prepared by the procedure described in Example 19 using 9.2 g of N-ethyl glycine, 10.2 g of 2-(trifluoromethyl)-phenyl-isothiocyanate, 10.1 g of triethylamine, and 150 mL of methylene chloride. The residue was further purified by flash chromatography on silica gel (methylene chloride). Crystallization from ethanol afforded the title compound (2.7 g), m.p. 82-85° C. Anal. Calcd. for. C_{12} H_{11} F_3 N_2 O S: C, 50.00; H, 3.85; N,9.72. Found: C, 50.00; H, 3.61; N, 9.61. Mass spectrum (EI, $M.^+$) *m/z* 288.

EXAMPLE 31

1-Ethyl-3-(2-ethyl-6-isopropylphenyl)-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 28 using 20.5 g of 2-ethyl-6-isopropylphenyl-isothiocyanate, 18.4 g of N-ethyl glycine, 20.2 g of triethyl amine, and 300 mL of chloroform. Purification was achieved by flash chromatography on silica gel (5-10 % ethyl acetate in hexane). Crystallization from diethyl ether/hexane afforded pure title compound (7.5 g) as a white solid, m.p. 77-79°

C. Anal. Calcd. for. $C_{16}H_{22}N_2OS$: C, 66.17; H, 7.64; N, 9.65. Found: C, 66.12; H, 7.77; N, 9.69. Mass spectrum (EI, $M.^+$) *m/z* 290.

EXAMPLE 32

1-Ethyl-3-(2-ethyl-6-methylphenyl)-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 28 using 17.7 g of 2-ethyl-6-methylphenyl-isothiocyanate, 18.4 g of N-ethyl glycine, 20.2 g of triethyl amine, and 300 mL of chloroform. The residue was further purified by flash chromatography on silica gel (20 % ethyl acetate in hexane).The title compound was obtained (8.6 g) as a light peach solid, m.p. 82-84° C. Anal. Calcd. for. $C_{14}H_{18}N_2OS$: C, 64.09; H, 6.92; N, 10.68. Found: C, 64.27; H, 7.04; N, 10.60. Mass spectrum (EI, $M.^+$) *m/z* 262.

EXAMPLE 33

3-(2-Chloro-4-methylphenyl)-1-ethyl-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 28 using 18.3 g of 2-chloro-4-methylphenyl-isothiocyanate, 18.4 g of N-ethyl glycine, 20.2 g of triethyl amine, and 300 mL of chloroform. Crystallization from ethyl acetate afforded the title compound (5.8 g) as a peach solid, m.p. 126-128° C. Anal. Calcd. for. $C_{12}H_{13}ClN_2OS$: C, 53.63; H, 4.88; N, 10.42. Found: C, 53.50; H, 4.76; N, 10.28. Mass spectrum (+FAB, $[M+H]^+$) *m/z* 269/271.

Example 34

1-Ethyl-3-[1-(4-fluorophenyl)-ethyl]-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 16 using 18.1 g of 1-(4-fluorophenyl)-ethyl-isothiocyanate, 18.4 g of N-ethyl glycine, 20.2 g of triethyl amine, and 300 mL of chloroform. Crystallization from ethyl acetate afforded the title compound (8.8 g) as a light yellow solid, m.p. 93-95° C. Anal. Calcd. for. $C_{13}H_{15}FN_2OS$: C, 58.63; H, 5.68; N, 10.52. Found: C, 58.69; H, 5.64; N, 10.58. Mass spectrum (EI, $M.^+$) *m/z* 266.

EXAMPLE 35

3-(2,4-Dichlorophenyl)-1-ethyl-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 16 using 20.4 g of 2,3-dichlorophenyl-isothiocyanate, 18.4 g of N-ethyl glycine, 20.2 g of triethyl amine, and 300 mL of chloroform. Purification was achieved by flash chromatography on silica gel (20 % ethyl acetate in hexane) The title compound (8.8 g) was obtained as a light peach solid, m.p. 144-146° C. Anal. Calcd. for. C_{11} H_{10} Cl_2 N_2 O S: C, 45.69; H, 3.49; N, 9.69. Found: C, 45.81; H, 3.40; N, 9.58. Mass spectrum (CI, $[M+H]^+$) *m/z* 289/291/293.

EXAMPLE 36

1-Ethyl-3-phenethyl-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 16 using 16.3 g of phenethyl-isothiocyanate, 18.4 g of N-ethyl glycine, 20.2 g of triethyl amine, and 300 mL of chloroform. Purification was achieved by flash chromatography on silica gel (20 % ethyl acetate in hexane) The title compound (15.0 g) was obtained as an off-white solid, m.p. 66-68° C. Anal. Calcd. for. C_{13} H_{16} N_2 O S: C, 62.87; H, 6.49; N, 11.28. Found: C, 63.03; H, 6.49; N, 11.32. Mass spectrum (EI, $M.^+$) *m/z* 248.

EXAMPLE 37

3-(2,3-Dimethylphenyl)-1-ethyl-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 16 using 16.3 g of 2,3-dimethylphenyl-isothiocyanate, 18.4 g of N-ethyl glycine, 20.2 g of triethyl amine, and 250 mL of chloroform. Crystallization from ethanol afforded the title compound (10.3 g) as a light pink solid, m.p. 120-121° C. Anal. Calcd. for. C_{13} H_{16} N_2 O S: C, 62.87; H, 6.49; N, 11.28. Found: C, 62.72; H, 6.44; N, 11.47. Mass spectrum (EI, $M.^+$) *m/z* 248.

EXAMPLE 38

3-(2,4-Dimethylphenyl)-1-ethyl-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 16 using 16.3 g of 2,4-dimethylphenyl-isothiocyanate, 18.4 g of N-ethyl glycine, 20.2 g of triethyl amine, and 250 mL of chloroform. Crystallization from ethanol afforded the title compound (10.8 g) as a light peach solid, m.p. 161-162° C. Anal. Calcd. for. C_{13} H_{16} N_2 O S: C,62.87; H, 6.49; N, 11.28. Found: C, 62.63; H, 6.45; N, 11.17. Mass spectrum (EI, $M.^+$) *m/z* 248.

EXAMPLE 39

3-(2,5-Dimethylphenyl)-1-ethyl-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 16 using 16.3 g of 2,5-dimethylphenyl-isothiocyanate, 18.4 g of N-ethyl glycine, 20.2 g of triethyl amine, and 250 mL of chloroform. Crystallization from ethyl acetate afforded the title compound (10.6 g) as an off-white solid, m.p. 176-178° C. Anal. Calcd. for. C_{13} H_{16} N_2 O S: C,62.87; H, 6.49; N, 11.28. Found: C, 62.70; H, 6.46; N, 11.27. Mass spectrum (EI, $M.^+$) *m/z* 248.

EXAMPLE 40

1-Ethyl-2-thioxo-3-(2,4,5-trimethylphenyl)-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 16 using 17.7 g of 2,4,5-trimethylphenyl-isothiocyanate, 18.4 g of N-ethyl glycine, 20.2 g of triethyl amine, and 250 mL of chloroform. Crystallization from ethanol afforded the title compound (15.3g) as an off-white solid, m.p. 162-164° C. Anal. Calcd. for. C_{14} H_{18} N_2 O S: C,64.09; H, 6.92; N, 10.68. Found: C, 64.21; H, 6.93; N, 10.80. Mass spectrum (EI, $M.^+$) *m/z* 262.

EXAMPLE 41

1-Ethyl-3-(2-isopropylphenyl)-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 16 using 15.42 g of 2-isopropylphenyl-isothiocyanate, 16.05 g of N-ethyl glycine, 12 g of triethyl amine, and 200 mL of chloroform. Purification was achieved by flash chromatography on silica gel (5-20 % ethyl acetate in hexane) Crystallization from ethanol afforded the title compound (9.8 g) as a white solid, m.p. 125-127° C. Anal. Calcd. for. C_{14} H_{18} N_2 O S: C, 64.09; H, 6.91; N, 10.68. Found: C, 64.19 H, 6.93; N, 10.71. Mass spectrum (EI, $M.^+$) *m/z* 262.

EXAMPLE 42

1-Ethyl-3-(2-ethylphenyl)-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 16 using 16.3 g of 2-ethylphenyl-isothiocyanate, 18.4 g of N-ethyl glycine, 20.2 g of triethyl amine, and 200 mL of chloroform. Purification was achieved by flash chromatography on silica gel (5-10 % ethyl acetate in hexane) Crystallization from diethyl ether afforded the title compound (9.12 g) as a white solid, m.p. 71-73° C. Anal. Calcd. for. C_{13} H_{16} N_2 O S: C,62.87; H, 6.49; N, 11.28. Found: C, 62.81; H, 6.43; N, 11.17. Mass spectrum (EI, $M.^+$) *m/z* 248.

EXAMPLE 43

3-(5-Chloro-2-methylphenyl)-1-phenyl-2-thioxo-imidazolidin-4-one

A mixture of N-phenyl glycine ethyl ester (8.95 g), 5-chloro-2-methylphenyl-isothiocyanate (9.18 g), and chloroform (200 mL) was heated at reflux for 24 hours. The solvent was evaporated. The residue was crystallized from ethyl acetate/hexane mixture. The solid was collected and dried to give 17.2 g of 2-[3-(5-chloro-2-methylphenyl)-1-phenyl-thioureido]-acetic acid ethyl ester as a white solid, m.p. 148-150° C. Anal. Calcd. for. C_{18} H_{19} Cl N_2 O_2 S: C, 59.58; H, 5.28; N, 7.72. Found: C, 59.79; H, 5.38; N, 7.65. Mass spectrum (EI, $M.^+$) *m/z* 262/264.

A mixture of 2-[3-(5-chloro-2-methylphenyl)-1-phenyl-thioureido]-acetic acid ethyl ester (9.5 g), triethyl amine (1 mL), and ethanol (150 mL) was heated at reflux for 2 hours. The mixture was concentrated to one-half volume and cooled to ambient temperature. The solid was collected and air dried to give the title compound (6.1 g) as an off-white solid, m.p. 168-170° C. Anal. Calcd. for. $C_{16}H_{13}ClN_2OS$: C, 60.66; H, 4.14; N, 8.84. Found: C, 60.81; H, 4.16; N, 8.81. Mass spectrum (EI, $M.^+$) *m/z* 316/318.

EXAMPLE 44

3-(3-Chloro-2-methylphenyl)-1-phenyl-2-thioxo-imidazolidin-4-one

A mixture of N-phenyl glycine ethyl ester (8.95 g), 3-chloro-2-methylphenyl-isothiocyanate (9.18 g), and chloroform (200 mL) was heated at reflux for 18 hours. The solvent was evaporated to dryness. The residue was mixed with ethanol (150 mL), and triethyl amine (3 mL). The mixture was heated at reflux for 3 hours. The solvent was evaporated. The residue was dissolved in ethyl acetate (300 mL) and washed with 1N HCl (2x200 mL), then with water (200 mL). The organic phase was dried over anhydrous magnesium sulfate and evaporated to dryness. The residue was treated with diethyl ether. The solid was collected by filtration and air dried to give the title compound (5.3 g) as an off-white solid, m.p. 154-156° C. Anal. Calcd. for. $C_{16}H_{13}ClN_2OS$: C, 60.66; H, 4.14; N, 8.84. Found: C, 60.48; H, 4.05; N, 8.76. Mass spectrum (+FAB, $[M+H]^+$) *m/z* 317/319.

EXAMPLE 45

3-(5-Chloro-2-methylphenyl)-1-isopropyl-2-thioxo-imidazolidin-4-one

2-Chloro acetic acid (69.0 g) was added portionwise while stirring to a isopropyl amine (431.5 g). The addition was carried over a period of 30 minutes. The mixture was stirred at ambient temperature for 18 hours. The excess isopropyl amine was evaporated leaving a viscous clear oil (182.0 g) which solidified upon standing. The crude product consisted of a 1:1 mixture of N-isopropyl glycine and isopropyl amine hydrochloride. This product mixture was used without further purification for the preparation of the title compound, in the next paragraph, and for preparation of the title compounds described in Example 46 through Example 52.

A mixture of the crude N-isopropyl glycine (21.2 g), 5-chloro-2-methylphenyl-isothiocyanate (18.3 g), triethyl amine (21.0 g) and chloroform (300 mL) was heated at reflux for 4 hours. The solvent was evaporated. The residue was dissolved in ethyl acetate (400 mL) and water (300 mL). The organic phase was washed with 2N HCl (2x300 mL), then with water. The organic phase was dried over anhydrous magnesium sulfate and evaporated to dryness. Crystallization from ethanol afforded the title compound (15.4 g) as a peach solid, m.p. 142-144° C. Anal. Calcd. for. C_{13} H_{15} Cl N_2 O S: C, 55.21; H, 5.35; N, 9.91. Found: C, 55.07; H, 5.20; N, 9.82. Mass spectrum (+FAB, $[M+H]^+$) *m/z* 283/285.

EXAMPLE 46

3-(2,6-Dimethylphenyl)-1-isopropyl-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 45 using 16.3 g of 2,6-dimethylphenyl-isothiocyanate, 21.2g of N-isopropyl glycine, 21.0 g of triethyl amine, and 300 mL of chloroform. Crystallization from ethanol afforded the title compound (12.9 g) as a white solid, m.p. 135-137° C. Anal. Calcd. for. C_{14} H_{18} N_2 O S: C, 64.09; H, 6.92; N, 10.68. Found: C, 63.99; H, 6.72; N, 10.67. Mass spectrum (+FAB, $[M+H]^+$) *m/z* 263.

EXAMPLE 47

3-(2,6-Diisopropylphenyl)-1-isopropyl-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 45 using 21.9 g of 2,6-diisopropylphenyl-isothiocyanate, 21.2 g of N-isopropyl glycine, 21.0 g of triethyl amine, and 300 mL of chloroform. Crystallization from ethanol afforded the title compound (11.7 g) as a white solid, m.p. 175-177° C. Anal. Calcd. for. C_{18} H_{26} N_2 O S: C, 67.88; H, 8.23; N, 8.80. Found: C, 68.03; H, 8.09; N, 8.81. Mass spectrum (+FAB, $[M+H]^+$) *m/z* 319.

EXAMPLE 48

3-(4-Fluorophenyl)-1-isopropyl-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 45 using 15.3 g of 4-fluorophenyl-isothiocyanate, 21.2 g of N-isopropyl glycine, 21.0 g of triethyl amine, and 300 mL of chloroform. Crystallization from ethanol afforded the title compound (12.6 g) as a peach solid, m.p. 184-186° C. Anal. Calcd. for. C_{12} H_{13} F N_2 O S: C, 57.12; H, 5.19; N, 11.10. Found: C, 56.98; H, 5.09; N, 11.06. Mass spectrum (+FAB, $[M+H]^+$) *m/z* 253.

EXAMPLE 49

3-(Indan-5-yl)-1-isopropyl-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 45 using 17.5 g of indan-5-yl-isothiocyanate, 21.2 g of N-isopropyl glycine, 21.0 g of triethyl amine, and 300 mL of chloroform. Crystallization from ethanol afforded the title compound (9.9 g) as a white solid, m.p. 178-180° C. Anal. Calcd. for. C_{15} H_{18} N_2 O S: C, 56.66; H, 6.61; N, 10.21. Found: C, 56.70; H, 6.67; N, 10.22. Mass spectrum (EI, $M.^+$) *m/z* 274.

EXAMPLE 50

3-(2-Ethyl-6-methylphenyl)-1-isopropyl-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 45 using 17.7 g of 2-ethyl-6-methylphenyl-isothiocyanate, 21.2 g of N-isopropyl glycine, 21.0 g of triethyl amine, and 300 mL of chloroform. Crystallization from ethanol afforded the title compound (13.0 g) as a light yellow solid, m.p. 132-134° C. Anal. Calcd. for. C_{15} H_{20} N_2 O S: C, 65.18; H, 7.29; N, 10.14. Found: C, 65.06; H, 7.37; N, 10.20. Mass spectrum (EI, $M.^+$) *m/z* 276.

EXAMPLE 51

3-(2-Ethylphenyl)-1-isopropyl-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 45 using 16.3 g of 2-ethylphenyl-isothiocyanate, 21.2 g of N-isopropyl glycine, 21.0 g of triethyl amine, and 300 mL of chloroform. Crystallization from diethyl ether afforded the title compound (6.8 g) as a white solid, m.p. 103-105° C. Anal. Calcd. for. C_{14} H_{18} N_2 O S: C, 64.09; H, 6.92; N, 10.68. Found: C, 64.08; H, 6.92; N, 10.62. Mass spectrum (EI, $M.^+$) *m/z* 262.

EXAMPLE 52

1-Isopropyl-3-(2-isopropylphenyl)-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 45 using 10.0 g of 2-isopropylphenyl-isothiocyanate, 11.9 g of N-isopropyl glycine, 12.0 g of triethyl amine, and 200 mL of chloroform. Crystallization from ethanol afforded the title compound (6.8 g) as a light pink solid, m.p. 112-114° C. Anal. Calcd. for. C_{15} H_{20} N_2 O S: C, 65.18; H, 7.29; N, 10.13. Found: C, 65.51; H, 7.25; N, 10.32. Mass spectrum (EI, $M.^+$) *m/z* 276.

EXAMPLE 53

1-Benzyl-3-(4-butylphenyl)-2-thioxo-imidazolidin-4-one

A mixture of N-benzyl glycine (8.7 g), 4-n-butylphenyl-isothiocyanate (8.55 g), triethyl amine (5.5 g) and chloroform (150 mL) was heated at reflux for 5 hours. The solvent was evaporated. The residue was dissolved in ethyl acetate (300 mL) and water (2x200 mL). The organic phase was dried over anhydrous magnesium sulfate and evaporated to dryness. Crystallization from ethyl acetate afforded the title compound (11.4 g) as an off-white solid, m.p. 149-151° C. Anal. Calcd. for. C_{20} H_{22} N_2 O S: C, 70.97; H, 6.55; N, 8.28. Found: C, 70.81; H, 6.76; N, 8.32. Mass spectrum (EI, $M.^+$) *m/z* 338.

EXAMPLE 54

1-Butyl-3-(5-chloro-2-methylphenyl)-2-thioxo-imidazolidin-4-one

2-Chloro acetic acid (47.3 g) was added portionwise while stirring to a n-butyl amine (500.0 g). The addition was carried over a period of 30 minutes. The mixture was stirred at ambient temperature for 18 hours. The excess n-butyl amine was evaporated leaving a viscous clear oil (120.0 g) which solidified upon standing. The crude product consisted of a 1:1 mixture of N-butyl glycine and butyl amine hydrochloride. This product mixture was used without further purification for the preparation of the title compound, in the next paragraph, and for preparation of the title compounds described in Example 55 and Example 56.

A mixture of N-butyl glycine (12.0 g), 5-chloro-2-methylphenyl-isothiocyanate (9.15 g), triethyl amine (12.0 g) and chloroform (200 mL) was heated at reflux for 5 hours. The solvent was evaporated. The residue was treated with diethyl ether (400 mL). The mixture was filtered. The solid was washed with diethyl ether then discarded. The filtrate was evaporated to dryness. Crystallization from ethanol afforded the title compound (6.0 g) as a tan solid, m.p. 102-103° C. Anal. Calcd. for. C_{14} H_{17} Cl N_2 O S: C, 56.65; H, 5.77; N, 9.44. Found: C, 56.41; H, 5.97; N, 9.36. Mass spectrum (EI, $M.^+$) *m/z* 296/298.

EXAMPLE 55

1-Butyl-3-(4-fluorophenyl)-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 54 using 7.7 g of 4-fluorophenyl-isothiocyanate, 12.0 g of N-butyl glycine, 15.0 g of triethyl amine, and 250 mL of chloroform. Crystallization from ethanol afforded the title compound (5.9 g) as an off-white solid, m.p. 92-93° C. Anal. Calcd. for. C_{13} H_{15} F N_2 O S: C, 58.62; H, 5.68; N, 10.52: Found: C, 58.23; H, 5.65; N, 10.56. Mass spectrum (EI, $M.^+$) *m/z* 266.

EXAMPLE 56

1-Butyl-3-(2-chloro-6-methylphenyl)-2-thioxo-imidazolidin-4-one

The title compound was prepared by the procedure described in Example 54 using 6.5 g of 2-chloro-6-methylphenyl-isothiocyanate, 8.5 g of N-butyl glycine, 10.0 g of triethyl amine, and 150 mL of methylene chloride. Purification was achieved by flash chromatography on silica gel (methylene chloride). Crystallization from ethanol afforded the title compound (3.85 g) as a light pink solid, m.p. 97-100° C. Anal. Calcd. for. C_{14} H_{17} Cl N_2 O S : C, 56.65; H, 5.77; N, 9.44. Found: C, 56.45; H, 5.67; N, 9.33. Mass spectrum (+FAB, $[M+H]^+$) *m/z* 297.

EXAMPLE 57

3-(4-t-Butylphenyl)-1-methyl-2-thioxo-imidazolidin-4-one

A mixture of sarcosine ethyl ester hydrochloride (7.68 g), 4-t-butylphenyl-isothiocyanate (9.6 g), triethyl amine (10.1 g) and chloroform (250 mL) was heated at reflux for 3 hours. The mixture was cooled to ambient temperature, washed with 2N HCl (2x200 mL), then with water (200 mL). The organic phase was dried over anhydrous magnesium sulfate and evaporated to dryness. The residue was crystallized from ethanol to give the title compound (9.9 g), m.p. 156-158° C. Anal. Calcd. for C_{14} H_{18} N_2 O S: C, 64.09; H, 6.91; N,10.68. Found: C, 63.83; H, 7.15; N, 10.53. Mass spectrum (EI, $M.^+$) *m/z* 262.

EXAMPLE 58

1-Ethyl-3-(2-methylsulfanylphenyl)-2-thioxo-imidazolidin-4-one

A mixture of N-ethyl glycine (9.23 g), 2-(methylthio)-phenyl-isothiocyanate (9.1 g), triethylamine (10.1 g) and methylene chloride (150 mL) was heated at reflux for 3 hours. The mixture was evaporated to dryness. The residue was recrystallized from ethanol to give the title compound (6.5 g) as a creamy solid, m.p. 128-131° C. Anal. Calcd. for. $C_{12}H_{14}N_2S_2O$: C, 52.11; H, 5.30; N, 10.52. Found: C, 52.28; H, 5.26; N, 10.54. Mass spectrum (EI, $M.^+$) *m/z* 266.

EXAMPLE 59

1-Allyl-3-(2,6-dimethylphenyl)-2-thioxo-imidazolidin-4-one

Chloroacetic acid (27.5 g) was added portionwise over 5 minutes to a cooled solution of allylamine (114 g) in water (100 mL). The reaction mixture was stirred at ambient temperature for 48 hours. The mixture was then evaporated to a viscous oily residue (35 g). The crude product consisted of a 1:1 mixture of N-allyl glycine and allyl amine hydrochloride. This product mixture was used without further purification for the preparation of the title compound, in the next paragraph, and for preparation of the title compound described in Example 60.

A mixture of N-allyl glycine (17.4 g), 2,6-dimethylphenyl-isothiocyanate (20 g), triethylamine (20.2 g), and methylene chloride (150 mL) was heated at reflux for 3 hours. The reaction mixture was evaporated to dryness. The residual gum was dissolved in diethyl ether, then treated with etheral hydrogen chloride. A white solid formed. The solid was filtered and discarded. The filtrate was concentrated to a residue. The residure was chromatographed on silica gel (CH_2Cl_2) to give title compound (5.2 g) as an orange solid, m.p. 43-46° C. Anal. Calcd. for. C_{14} H_{16} N_2 OS: C, 64.59; H, 6.19; N, 10.76. Found: C, 64.52; H, 6.08; N, 10.66. Mass spectrum (EI, $M.^+$) *m/z* 260.

EXAMPLE 60

1-Allyl-3-(5-chloro-2-methylphenyl)-2-thioxo-imidazolidin-4-one

A mixture of N-allyl glycine (17.4 g), 5-chloro-2-methylphenyl-isothiocyanate (20.1 g), triethylamine (20.2 g), and methylene chloride (150 mL) was heated at reflux for 2 hours. The reaction mixture was evaporated to dryness. Purification was achieved by flash chromatography on silica gel (methylene chloride). Recrystallization from Hexane-EtOAc afford the title compound (4.8 g) as yellow solid, m.p. 106-109° C. Anal. Calcd. for. C_{13} H_{13} N_2 O Cl S: C, 55.61; H, 4.67; N, 9.98. Found: C, 55.45; H, 4.56; N, 9.72. Mass spectrum (EI, $M.^+$) *m/z* 280.

EXAMPLE 61

3-(2,6-dimethylphenyl)-1-(prop-2-ynyl)-2-thioxo-imidazolidin-4-one

To a cooled solution of ethyl bromoacetate (37.6 g) in diethyl ether (75 mL), was added propargylamine (25 g). The mixture was stirred for 3 hour at 0-5° C. The reaction temperature was raised to ambient temperature, and the stirring continued for 18 hours. A solid formed. The solid was filtered and discarded. The filtrate was evaporated to dryness to give crude title compound (30.1 g). The crude product was used without further purification for the preparation of the title compound, in the next paragraph, and for preparation of the title compounds described in Example 62 and Example 63.

A mixture of ethyl N-propargylaminoacetate (14.1 g), 2,6-dimethylphenyl-isothiocyanate (16.3 g), triethylamine (10.1 g), and methylene chloride (150 mL) was heated at reflux for 3 hours. The reaction mixture was cooled to ambient temperature, washed with 1N HCl (100 mL), then with water. The organic layer was separated, dried over anhydrous magnesium sulfate, then evaporated to dryness. The residual oil was triturated with hexane. The solid was collected by filtration. Recrystallization from hexane-EtOAc afforded the title compound (12.5 g) as yellow solid, m.p. 117-121° C. Anal. Calcd. for. C_{14} $H_{14}N_2S_2$ O: C, 65.09; H, 5.46; N, 10.84. Found: C, 65.23; H, 5.43; N, 10.88. Mass spectrum (EI, $M.^+$) *m/z* 258.

EXAMPLE 62

3-(5-chloro-2-methylphenyl)-1-(prop-2-ynyl)-2-thioxo-imidazolidin-4-one

A mixture of ethyl N-propargylaminoacetate (7.0 g), 5-chloro-2-methylphenylisothiocyanate (9.2 g), triethylamine (5.0 g), and methylene chloride (100 mL) was heated at reflux for 3 hours. The reaction mixture was cooled to ambient temperature, washed with 1 N HCl (50 mL), then with water. The organic layer was dried over anhydrous magnesium sulfate, then evaporated to dryness. The residual oil was triturated with hexane. The solid was collected by filtration. Recrystallization from EtOAc afford the title compound (5.1 g) as yellow solid, m.p.

131-134° C. Anal. Calcd. for. C_{13} H_{11} N_2 O Cl S: C, 56.01; H, 3.98; N, 10.05. Found: C, 55.90; H, 3.77; N, 9.92. Mass spectrum (EI, $M.^+$) *m/z* 278.

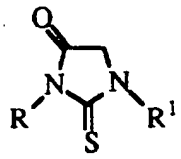
EXAMPLE 63

3-(4-chloro-2-methylphenyl)-1-(prop-2-ynyl)-2-thioxo-imidazolidin-4-one

A mixture of ethyl N-propargylaminoacetate (10.0 g), 4-chloro-2-methylphenylisothiocyanate (12.9 g), triethylamine (7.1 g), and methylene chloride (150 mL) was heated at reflux for 3 hours. The reaction mixture was cooled to ambient temperature, washed with 1 N HCl (100 mL), then with water. The organic layer was dried over anhydrous magnesium sulfate, then evaporated to dryness. The residual oil was triturated with hexane. The solid was collected by filtration. Recrystallization from Hexane-EtOAc afford the title compound (5.2 g) as yellow solid, m.p. 99-102° C. Anal. Calcd. for. C_{13} H_{11} N_2 O Cl S: C, 56.01; H, 3.98; N, 10.05. Found: C, 55.61; H, 3.83; N, 10.0. Mass spectrum (EI, $M.^+$) *m/z* 278.

CLAIMS

(1) A compound of formula I:



I

wherein

R is alkyl of 1 to 6 carbon atoms; a substituted or unsubstituted aromatic N, O or S heterocycle having 4 to 6 carbon and one hetero ring members; substituted or unsubstituted aryl of 6 to 10 carbon atoms, arylalkyl of 7 to 12 carbon atoms, benzhydryl or indanyl, in which the substituents are one to three members independently selected from the group consisting of alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkylthio of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, alkynyl of 2 to 6 carbon atoms, halo, perfluoroalkyl of 1 to 6 carbon atoms, perfluoroalkoxy of 1 to 6 carbon atoms or hydroxy; and

R^1 is aryl of 6 to 10 carbon atoms, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, alkynyl of 2 to 6 carbon atoms or substituted aryl of 6 to 10 carbon atoms where the substituents are one to three members independently selected from the group consisting of alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon ations, alkylthio of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, alkynyl of 2 to 6 carbon atoms, halo, perfluoroalkyl of 1 to 6 carbon atoms, perfluoroalkoxy of 1 to 6 carbon atoms or hydroxy, for use in the treatment of mammals.

(2) A compound according to claim 1 wherein the treatment is for increasing the HDL cholesterol concentration in the blood of a mammal in need of increased HDL cholesterol blood concentration.

(3) A compound of Claim 1 or 2 in which said compound is of formula I in which R is substituted phenyl where the substituents are two members of the group consisting of alkyl of 1 to 6 carbon atoms,perfluoroalkoxy of 1 to 6 carbon atoms, halo, or ortho

substituted trimethylene or tetramethylene and R^1 is alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms or alkynyl of 2 to 6 carbon atoms.

(4) A compound of Claim 1 or 2 in which said compound is of formula I in which R is substituted phenyl where the substituents are a halo and an alkyl group of 1 to 3 carbon atoms or ortho substituted trimethylene and R^1 is alkyl of 1 to 3 carbon atoms, alkenyl of 2 to 4 carbon atoms or alkynyl of 2 to 4 carbon atoms.

(5) A compound of Claim 1 or 2 in which said compound is of formula I in which R is substituted phenyl where the substituents are chloro or fluoro in the 4- or 5-position and an alkyl group of 1 to 3 carbon atoms and R^1 is alkyl of 1 to 3 carbon atoms, alkenyl of 2 to 4 carbon atoms or alkynyl of 2 to 4 carbon atoms.

(6) A compound of Claim 1 or 2 in which said compound is selected from the group consisting of:

3-(5-Chloro-2-methylphenyl)-1-methyl-2-thioxo-imidazolidin-4-one;
3-(3-Chloro-2-methylphenyl)-1-methyl-2-thioxo-imidazolidin-4-one;
3-(4-Chloro-2-methylphenyl)-1-methyl-2-thioxo-imidazolidin-4-one;
3-(Indan-5-yl)-1-methyl-2-thioxo-imidazolidin-4-one;
3-(2,6-Diisopropylphenyl)-1-methyl-2-thioxo-imidazolidin-4-one;
3-(2-Ethyl-6-isopropylphenyl)-1-methyl-2-thioxo-imidazolidin-4-one;
3-(2-Ethyl-6-methylphenyl)-1-methyl-2-thioxo-imidazolidin-4-one;
3-(5-Chloro-2-methylphenyl)-1-ethyl-2-thioxo-imidazolidin-4-one;
3-(2,6-Dichlorophenyl)-1-ethyl-2-thioxo-imidazolidin-4-one;
1-Ethyl-3-(4-fluorophenyl)-2-thioxo-imidazolidin-4-one;
1-Ethyl-2-thioxo-3-(4-trifluoromethoxyphenyl)-imidazolidin-4-one;
3-(2,6-Dimethylphenyl)-1-ethyl-2-thioxo-imidazolidin-4-one;
1-Ethyl-3-isobutyl-2-thioxo-imidazolidin-4-one;
3-(2-Chlorophenyl)-1-ethyl-2-thioxo-imidazolidin-4-one;
1-Ethyl-3-(2-tolyl)-2-thioxo-imidazolidin-4-one;
3-(2-Chloro-6-methylphenyl)-1-ethyl-2-thioxo-imidazolidin-4-one;
1-Ethyl-3-(5-fluoro-2-methylphenyl)-2-thioxo-imidazolidin-4-one;
3-(2,6-Diisopropylphenyl)-1-ethyl-2-thioxo-imidazolidin-4-one;

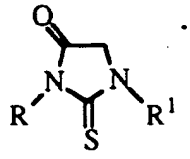
1-Ethyl-2-thioxo-3-(2-trifluoromethylphenyl)-imidazolidin-4-one;
1-Ethyl-3-(2-chloro-6-methylphenyl)-2-thioxo-imidazolidin-4-one;
3-(2-Ethyl-4-methylphenyl)-1-ethyl-2-thioxo-imidazolidin-4-one;
3-(2,4-Dichlorophenyl)-1-ethyl-2-thioxo-imidazolidin-4-one;
3-(2,4-Dimethylphenyl)-1-ethyl-2-thioxo-imidazolidin-4-one;
3-(2,5-Dimethylphenyl)-1-ethyl-2-thioxo-imidazolidin-4-one;
1-Ethyl-2-thioxo-3-(2,4,5-trimethylphenyl)-imidazolidin-4-one;
1-Ethyl-3-(2-isopropylphenyl)-2-thioxo-imidazolidin-4-one;
1-Ethyl-3-(2-ethylphenyl)-2-thioxo-imidazolidin-4-one;
3-(5-Chloro-2-methylphenyl)-1-phenyl-2-thioxo-imidazolidin-4-one;
3-(5-Chloro-2-methylphenyl)-1-isopropyl-2-thioxo-imidazolidin-4-one;
3-(2,6-Dimethylphenyl)-1-isopropyl-2-thioxo-imidazolidin-4-one;
3-(2-Ethyl-6-methylphenyl)-1-isopropyl-2-thioxo-imidazolidin-4-one;
1-Butyl-3-(4-fluorophenyl)-2-thioxo-imidazolidin-4-one;
1-Allyl-3-(2,6-dimethylphenyl)-2-thioxo-imidazolidin-4-one;
3-(2,6-Dimethylphenyl)-1-(prop-2-ynyl)-2-thioxo-imidazolidin-4-one;
3-(3-Chloro-4-methylphenyl)-1-methyl-2-thioxo-imidazolidin-4-one
3-(2-Ethylphenyl)-1-methyl-2-thioxo-imidazolidin-4-one
1-Methyl-3-(2-isopropylphenyl)-2-thioxo-imidazolidin-4-one
3-(4-t-Butylphenyl)-1-methyl-2-thioxo-imidazolidin-4-one
1-Allyl-3-(5-chloro-2-methylphenyl)-2-thioxo-imidazolidin-4-one
3-(5-Chloro-2-methylphenyl)-1-(prop-2-ynyl)-2-thioxo-imidazolidin-4-one; or
1-Ethyl-3-(2-ethyl-6-isopropylphenyl)-2-thioxo-imidazolidin-4-one.
3-(2-chloro-6-methylphenyl)-1-methyl-2-thioxo-imidazolidin-4-one.
3-(2,6-dimethylphenyl)-1-methyl-2-thioxo-imidazolidin-4-one.

(7) Use of a compound of formula I as defined in any of claims 1 to 6 for the manufacture of a medicament for increasing the HDL cholesterol concentration in the blood of a mammal in need of increased HDL cholesterol blood concentration.

(8) A pharmaceutical composition comprising a compound of the formula I as defined in any of claims 1 to 6 and a pharmaceutically acceptable carrier.

(9) A method for increasing the HDL cholesterol concentration in the blood of a mammal in need of increased HDL cholesterol blood concentration, which comprises administering to said mammal, orally or parenterally, a compound of formula I as defined in any of claims 1 to 6.

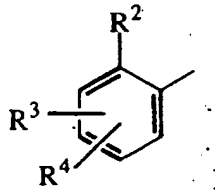
(10) A compound of formula I:



I

wherein

R^1 is alkyl of 1 to 6 carbon atoms and R is alkyl of 1 to 6 carbon atoms, naphthyl, benzhydryl, fluorophenylmethyl, phenethyl, 1-(fluorophenyl)ethyl, 5-chloro-2-methoxyphenyl, trifluoromethoxyphenyl, trifluoromethylphenyl, methylsulfanylphenyl, pyridyl or the group of formula II



II

where R^2, R^3 and R^4 together are 2-chloro, 4-fluoro, 2,4-chloro or 2,6- chloro, or R^2 is hydrogen, R^3 is a halogen in 3-position and R^4 is alkyl of 1 to 6 carbon atoms in 4-position, or R^2 is alkyl of 1 to 6 carbon atoms and R^3 and R^4 are, independently, hydrogen or alkyl of 1 to 6 carbon atoms or R^3 is a halogen and R^4 is hydrogen;

or

R^1 is alkenyl of 2 to 6 carbon atoms, R is is the group of formula II

where R^2 is alkyl of 1 to 6 carbon atoms and R^3 and R^4 are, independently, hydrogen or alkyl of 1 to 6 carbon atoms, or R^2 is hydrogen and R^3 and R^4 taken together are ortho substituted trimethylene or tetramethylene, or R^2 is alkyl of 1 to 6 carbon atoms,

R^3 is halogen and R^4 is hydrogen, or R^2 is hydrogen, R^3 is halogen in 3-position and R^4 is alkyl of 1 to 6 carbon atoms in 4-position;

or

when R^1 is alkynyl of 2 to 6 carbon atoms, R is a group of formula II

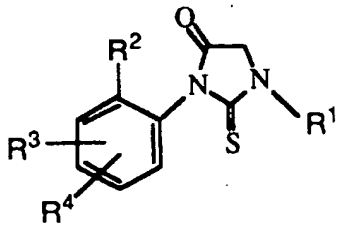
where any two of R^2, R^3 and R^4 are, independently, alkyl of 1 to 6 carbon atoms, halo, perfluoralkyl of 1 to 6 carbon atoms, perfluoralkoxy of 1 to 6 carbon atoms, or, taken together, are ortho substituted trimethylene or tetramethylene;

or

when R^1 is aryl of 6 to 10 carbon atoms or arylalkyl of 7 to 12 carbon atoms, R is the group of formula II

where R^2 is alkyl of 1 to 6 carbon atoms, R^3 is a halogen and R^4 is hydrogen, or R^2 is hydrogen, R^3 is a halogen in 3-position and R^4 is alkyl of 1 to 6 carbon atoms in 4-position.

(11) A compound according to Claim 10 of formula:



in which

R^1 is alkyl of 1 to 6 carbon atoms or alkenyl of 2 to 6 carbon atoms;

R^2 is alkyl of 1 to 6 carbon atoms and R^3 and R^4 are, independently, hydrogen or alkyl of 1 to 6 carbon atoms; or R^2 is hydrogen and R^3 and R^4 taken together are ortho substituted trimethylene or tetramethylene.

(12) A compound according to Claim 11 in which R^3 and R^4 are hydrogen, R^1 is methyl or ethyl and R^2 is alkyl of 1 to 3 carbon atoms.

(13) The compound according to Claim 11 or 12 which is 3-(2-ethylphenyl)-1-methyl-2-thioxo-imidazolidin-4-one.

1-methyl-3-(2-isopropylphenyl)-2-thioxo-imidazolidin-4-one.
1-ethyl-3-(2-tolyl)-2-thioxo-imidazolidin-4-one.
1-ethyl-3-(2-isopropylphenyl)-2-thioxo-imidazolidin-4-one.
1-ethyl-3-(2-ethylphenyl)-2-thioxo-imidazolidin-4-one.

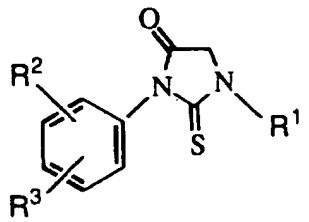
(14) A compound according to Claim 11 in which R^4 is hydrogen , R^1 is methyl, ethyl or allyl, R^2 is alkyl of 1 to 3 carbon atoms and R^3 is alkyl of 1 to 3 carbon atoms or R^2 is hydrogen and R^3 and R^4 are ortho substituted trimethylene or tetramethylene.

(15) The compound according to Claim 14 which is
3-(2-ethyl-6-methylphenyl)-1-methyl-2-thioxo-imidazolidin-4-one.
3-(2,6-dimethylphenyl)-1-ethyl-2-thioxo-imidazolidin-4-one.
3-(2,6-dimethylphenyl)-1-isopropyl-2-thioxo-imidazolidin-4-one .
1-allyl-3-(2,6-dimethylphenyl)-2-thioxo-imidazolidin-4-one.
3-(2-ethyl-6-isopropylphenyl)-1-methyl-2-thioxo-imidazolidin-4-one.
1-ethyl-3-(2-ethyl-6-isopropylphenyl)-2-thioxo-imidazolidin-4-one.

(16) A compound according to Claim 11 in which R^1 is methyl, ethyl or allyl and R^2, R^3 and R^4 are , independently, alkyl of 1 to 3 carbon atoms.

(17) A compound according to Claim 16 which is 1-ethyl-2-thioxo-3-(2,4,5-trimethylphenyl)-imidazolidin-4-one.

(18) A compound according to Claim 10 of formula :



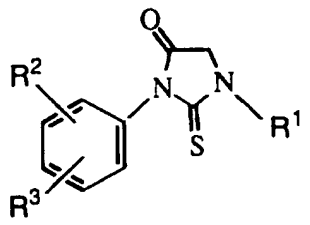
in which

R^1 is alkyl of 1 to 6 carbon atoms;

R^2 and R^3 represent 2,4-dichloro or 2,6-dichloro;
or R^2 is 2-chloro or 4-fluoro and R^3 is hydrogen.

(19) The compound according to Claim 18 which is
3-(2,6-dichlorophenyl)-1-ethyl-2-thioxo-imidazolidin-4-one;
1-ethyl-3-(4-fluorophenyl)-2-thioxo-imidazolidin-4-one;
3-(2-chlorophenyl)-1-ethyl-2-thioxo-imidazolidin-4-one;
3-(2,4-dichlorophenyl)-1-ethyl-2-thioxo-imidazolidin-4-one;
3-(4-fluorophenyl)-1-isopropyl-2-thioxo-imidazolidin-4-one;
1-butyl-3-(4-fluorophenyl)-2-thioxo-imidazolidin-4-one.

(20) A compound according to Claim 10 of formula:

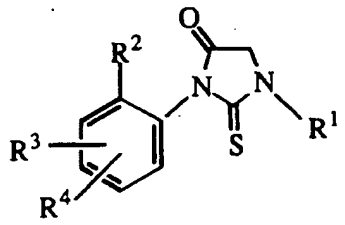


in which
R^1 is alkynyl of 2 to 6 carbon atoms; and
R^2 and R^3 are, independently, alkyl of 1 to 6 carbon atoms, halo, perfluoralkyl of 1 to 6 carbon atoms, perfluoralkoxy of 1 to 6 carbon atoms, or, taken together, R^2 and R^3 are ortho substituted trimethylene or tetramethylene.

(21) A compound of according to Claim 20 in which R^1 is ethynyl, propargyl or butynyl.

(22) The compound according to Claim 20 or 21 which is
3-(2,6-dimethylphenyl)-1-(prop-2-ynyl)-2-thioxo-imidazolidin-4-one;
3-(5-chloro-2-methylphenyl)-1-(prop-2-ynyl)-2-thioxo-imidazolidin-4-one;
3-(4-chloro-2-methylphenyl)-1-(prop-2-ynyl)-2-thioxo-imidazolidin-4-one;

(23) A compound according to Claim 10 of formula:



in which

R^1 is alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, aryl of 6 to 10 carbon atoms or arylalkyl of 7 to 12 carbon atoms;

R^2 is alkyl of 1 to 6 carbon atoms, R^3 is a halogen and R^4 is hydrogen; or

R^2 is hydrogen, R^3 is a halogen in 3-position and R^4 is alkyl of 1 to 6 carbon atoms in 4-position.

(24) A compound according to Claim 23 in which R^1 is alkyl of 1 to 3 carbon atoms, allyl or phenyl, R^2 is alkyl of 1 to 3 carbon atoms, R^3 is chloro or fluoro and R^4 is hydrogen.

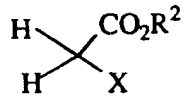
(25) The compound according to Claim 23 or 24 which is
3-(5-chloro-2-methylphenyl)-1-methyl-2-thioxo-imidazolidin-4-one.
3-(3-chloro-2-methylphenyl)-1-methyl-2-thioxo-imidazolidin-4-one.
3-(4-chloro-2-methylphenyl)-1-methyl-2-thioxo-imidazolidin-4-one.
3-(5-chloro-2-methylphenyl)-1-ethyl-2-thioxo-imidazolidin-4-one.
3-(2-chloro-6-methylphenyl)-1-ethyl-2-thioxo-imidazolidin-4-one.
1-ethyl-3-(5-fluoro-2-methylphenyl)-2-thioxo-imidazolidin-4-one.
3-(5-chloro-2-methylphenyl)-1-phenyl-2-thioxo-imidazolidin-4-one.
3-(5-chloro-2-methylphenyl)-1-isopropyl-2-thioxo-imidazolidin-4-one.
1-Allyl-3-(5-chloro-2-methylphenyl)-2-thioxo-imidazolidin-4-one

(26) A compound according to Claim 10 of formula I in which R^1 is alkyl of 1 to 6 carbon atoms; and R is alkyl of 1 to 6 carbon atoms, naphthyl, benzhydryl, fluorophenylmethyl, phenethyl, 1-(fluorophenyl)ethyl, 5-chloro-2-methoxyphenyl, trifluoromethoxyphenyl, trifluoromethylphenyl, methylsulfanylphenyl or pyridyl.

(27) A compound according to Claim 26 in which R^1 is alkyl of 1 to 6 carbon atoms; and R is alkyl of 1 to 6 carbon atoms, 2-naphthyl, benzhydryl, 4-fluorophenylmethyl, phenethyl, 1-(4-fluorophenyl)ethyl, 5-chloro-2-methoxyphenyl, 4-trifluoromethoxyphenyl, 2-trifluoromethylphenyl, 2-methylsulfanylphenyl or 3-pyridyl.

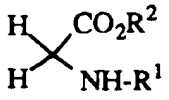
(28) The compound according to Claim 26 or 27 which is
3-benzhydryl-1-methyl-2-thioxo-imidazolidin-4-one;
1-methyl-3-(pyridin-3-yl)-2-thioxo-imidazolidin-4-one;
3-(5-chloro-2-methoxyphenyl)-1-methyl-2-thioxo-imidazolidin-4-one;
3-(5-chloro-2-methoxyphenyl)-1-ethyl-2-thioxo-imidazolidin-4-one;
1-ethyl-2-thioxo-3-(4-trifluoromethoxyphenyl)-imidazolidin-4-one;
1-ethyl-3-(4-fluorobenzyl)-2-thioxo-imidazolidin-4-one;
1-ethyl-3-isobutyl-2-thioxo-imidazolidin-4-one;
1-ethyl-3-(naphthalen-2-yl)-2-thioxo-imidazolidin-4-one;
1-ethyl-2-thioxo-3-(2-trifluoromethylphenyl)-imidazolidin-4-one;
1-ethyl-3-[1-(4-fluorophenyl)-ethyl]-2-thioxo-imidazolidin-4-one;
1-ethyl-3-phenethyl-2-thioxo-imidazolidin-4-one;
1-ethyl-3-(2-methylsulfanylphenyl)-2-thioxo-imidazolidin-4-one.

(29) Process for the preparation of a compound as defined in any of claims 1 to 28 comprising reacting the corresponding compound of formula A



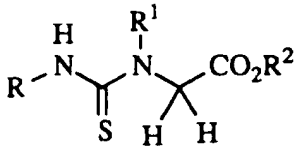
(A)

in which R^2 is as defined in any of claims 1 to 28 and X is halogen, with R^1-NH_2 in which R^1 is as defined in any of claims 1 to 28, to give a compound of formula 2(a)



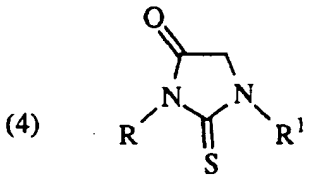
(2a)

in which R^1 and R^2 are as previously defined herein and reacting the compound of formula 2(a) with R-NCS in the presence of a base to provide either the compound of formula (3a)



(3a)

or of formula (4)



(4)

and thereafter cyclising the compound of formula (3a) to the compound of formula (4) by refluxing in the presence of a base.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/US 96/19164

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D233/86 C07D401/04 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 112, no. 10, 5 March 1990 Columbus, Ohio, US; abstract no. 079441, TANAKA A ET AL: "Photographic spectral sensitizers" XP002027619 see abstract; and Chemical Abstracts, CHEMICAL SUBSTANCES, 12th Collective Index, vol. 106-115, 1987-1991, page 46079CS: RN [125219-50-3] & JP 01 187 543 A (MITSUBISHI PAPER MILLS, LTD.;JAPAN) 26 July 1989 --- -/--	10,26-28

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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1

Date of the actual completion of the international search	Date of mailing of the international search report
14 March 1997	24.03.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Fink, D

Form PCT ISA 210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 96/19164

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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